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L1 STRUCTURE UPLOADED

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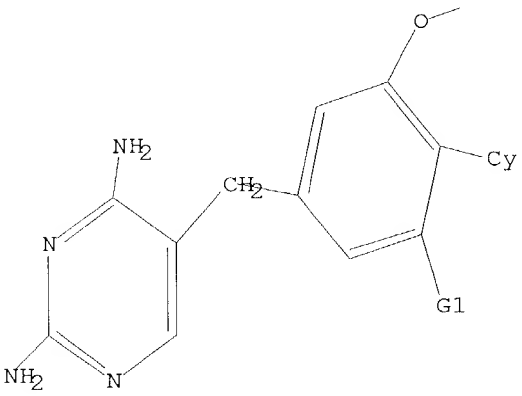
L1 HAS NO ANSWERS
L1 STR



G1 EtO,n-PrO,i-PrO,n-BuO,i-BuO,s-BuO,t-BuO

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full
FULL SEARCH INITIATED 18:32:00 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2423 TO ITERATE

100.0% PROCESSED 2423 ITERATIONS 197 ANSWERS
SEARCH TIME: 00.00.01

L2 197 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.42	155.90

FILE 'CAPLUS' ENTERED AT 18:32:08 ON 05 MAR 2004
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FILE COVERS 1907 - 5 Mar 2004 VOL 140 ISS 11
FILE LAST UPDATED: 4 Mar 2004 (20040304/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 40 L2

=> d l3 1-40 ibib abs hitstr

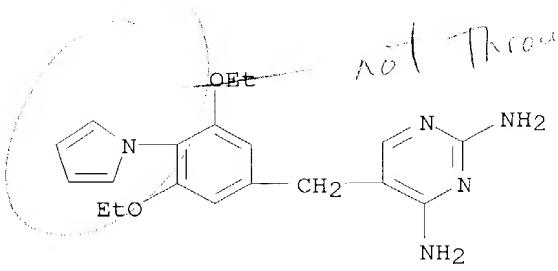
L3 ANSWER 1 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:906396 CAPLUS
DOCUMENT NUMBER: 139:332324
TITLE: Interaction energy analysis of nonclassical antifolates with Pneumocystis carinii dihydrofolate reductase
AUTHOR(S): Pitts, Conrad; Yin, Jian; Bowen, Donnell; Maxwell, Celia J.; Southerland, William M.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Howard University College of Medicine, Washington, DC, 20059, USA
SOURCE: International Journal of Molecular Sciences (2002), 3(11-12), 1188-1202
CODEN: IJMCFK; ISSN: 1422-0067
URL: http://www.mdpi.org/ijms/papers/i3111188.pdf
PUBLISHER: Molecular Diversity Preservation International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The x-ray structure of the Pneumocystis carinii dihydrofolate reductase (DHFR):trimethoprim:NADPH ternary complex obtained from the Protein Databank was used as a structural template to generate models for the following complexes: P. carinii DHFR:piritrexim:NADPH, P. carinii DHFR:epiroprim:NADPH, and P. carinii DHFR:trimetrexate:NADPH. Each of these complexes, including the original trimethoprim complex was then modeled in 60 angstrom cubes of explicit water and minimized to a rms gradient between 1.0 to 3.0 x 10-5 kcal/angstrom. Subsequently, each antifolate structure was subdivided into distinct substructural regions. The minimized complexes were used to calculate interaction energies for each intact antifolate and its corresponding substructural regions with the P. carinii DHFR binding site residues, the DHFR protein, the solvated complex (which consists of P. carinii DHFR, NADPH, and solvent water), solvent water alone, and NADPH. Antifolate substructural regions which contained nitrogen and carbonatoms in an aromatic environment (i.e. the pteridyl, pyridopyrimidinyl, and diaminopyrimidinyl subregions) contributed most to the stability of antifolate interactions, while interaction energies for the hydrocarbon aromatic rings, methoxy, and ethoxy groups were much less stable. Addnl., interaction energy analyses were calculated for carbonand nitrogen atoms of the pteridyl, pyridopyrimidinyl, and diaminopyrimidinyl subregion sand for the carbon and oxygen atoms of methoxy and ethoxy subregions. The contributions of hydrogen atoms were included with those of the carbon, nitrogen and oxygen atoms to which they are attached. These analyses revealed that the carbon atoms of the pteridyl, pyridopyrimidinyl, and diaminopyrimidinyl subregions generally contributed most to the stability of those regions. Carbon atoms also contributed favorably to the stability of the methoxy group interactions. Those substructural regions which exhibit relatively unfavorable interaction energies may constitute important modification targets in the design of

improved P. carinii DHFR inhibitors. Interaction energies for different groups of atoms within the substructural regions suggest strategies for modification of the substructural regions.

IT **73090-70-7**, Epiroprim
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(complexes with antifolates and NADPH; interaction energy anal. of nonclassical antifolates with Pneumocystis carinii dihydrofolate reductase)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:797511 CAPLUS

DOCUMENT NUMBER: 140:156670

TITLE: Physiologically based pharmacokinetic (PBPK) modeling of disposition of epiroprim in humans

AUTHOR(S): Luttringer, Olivier; Theil, Frank-Peter; Poulin, Patrick; Schmitt-Hoffmann, Anne H.; Guentert, Theodor Walter; Lave, Thierry

CORPORATE SOURCE: Pharma Research, Department of Non-Clinical Drug Safety, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.

SOURCE: Journal of Pharmaceutical Sciences (2003), 92(10), 1990-2007
CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

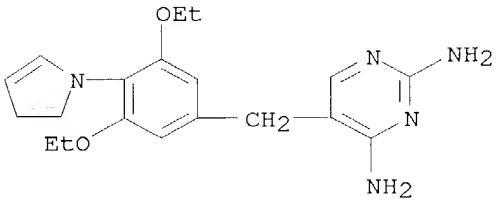
AB The objective of this study was to use in synergy physiol. based and empirical approaches to estimate the drug-specific input parameters of PBPK models of disposition to simulate the plasma concentration-time profile of epiroprim in human. The estimated input parameters were the tissue:plasma partition coeffs. (Pt:p) for distribution and the blood clearance (CL) for the in vivo conditions. Epiroprim represents a challenge for such methods, because it shows large interspecies differences in its pharmacokinetic properties. Two approaches were used to predict the human Pt:p values: the tissue composition model (TCM) and the "Arundel approach" based on the volume of distribution at steady state (Vdss) determined in vivo in the rat. CL in human was predicted by (1) conventional allometric scaling of in vivo animal clearances (CAS), (2) physiol. based direct scaling up of in vitro hepatocyte data (DSU), and (3) allometric scaling of animal intrinsic in vivo blood CL normalized by the ratios of animal:human intrinsic clearances determined in vitro with hepatocytes (NAS). The performance of prediction was assessed by comparing sep. the above pharmacokinetic parameters (Vdss estimated from the Pt:p values and blood CL)

with the corresponding in vivo data obtained from the plasma kinetic profiles. These input parameters were used in PBPK models, and the resulting plasma concentration-time profiles of epiroprim were compared with those observed in rat and human. Previously to the construction of the human PBPK model, a model for the rat was also developed to gain more confidence on the model structure and assumptions. Overall, using the TCM and the NAS for the parameterization of the distribution and clearance, resp., the PBPK model gave the more accurate predictions of epiroprim's disposition in human. This study represents therefore an attractive approach, which may potentially help the clin. candidate selection.

IT **73090-70-7**, Epiroprim
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(physiol. based pharmacokinetic (PBPK) modeling of disposition of epiroprim in humans)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202681 CAPLUS
DOCUMENT NUMBER: 138:236926
TITLE: A method for the treatment or prevention of bone erosion
INVENTOR(S): Ogawa, Yukie; Fukuda, Chie; Ohtsuki, Masahiko
PATENT ASSIGNEE(S): Sankyo Company, Limited, Japan
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020768	A1	20030313	WO 2002-JP8630	20020827

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

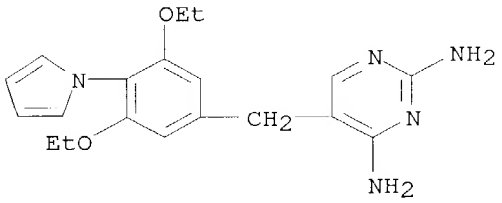
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,

NE, SN, TD, TG
JP 2003146903 A2 20030521 JP 2002-244432 20020826
PRIORITY APPLN. INFO.: JP 2001-257436 A 20010828

AB There is provided a method for the treatment or prevention of bone erosion caused by a disease that activates osteoclasts (e.g. rheumatoid arthritis) comprising administering to a patient an anti-human Fas monoclonal antibody HFE7A or a humanized version the antibody and anti-inflammatory agents. There is also provided a method for testing a substance for the treatment or prevention of bone erosion comprising: transplanting pieces of dentin and synovial tissue from a patient suffering from a disease that activates osteoclasts to immunodeficient non-human mammals; administering the substance to be tested to at least one of the test animals and a control to at least one different test animal and breeding them; and then extracting said pieces of dentin from the test animals and counting the number of resorption pits formed on the surface of each piece that was in contact with said sample of synovial tissue.

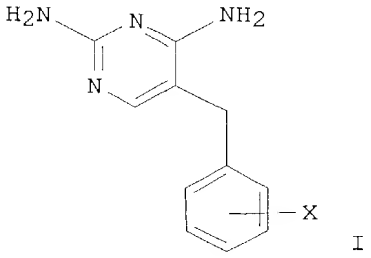
IT **73090-70-7,** Epiroprim
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-Fas monoclonal antibodies and anti-inflammatory agents in the treatment and prevention of bone erosion from osteoclasts)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:326190 CAPLUS
DOCUMENT NUMBER: 137:232199
TITLE: QSAR for dihydrofolate reductase inhibitors with molecular graph structural descriptors
AUTHOR(S): Ivanciuc, Ovidiu; Ivanciuc, Teodora; Cabrol-Bass, Daniel
CORPORATE SOURCE: Department of Marine Sciences, Texas A & M University at Galveston, Galveston, TX, 77551, USA
SOURCE: THEOCHEM (2002), 582, 39-51
CODEN: THEODJ; ISSN: 0166-1280
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



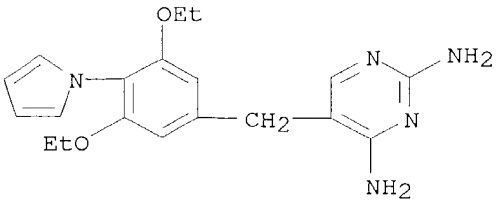
I

AB Mol. graph descriptors are used, together with a large diversity of geometric, electrostatic, and quantum indexes, to model phys., chemical, or biol. properties with quant. structure-property relationships and quant. structure-activity relationships of compds. I (X = H, 4-NO2, 3-F, 4-NH2, 4-F, 3-OH, etc). The interest of developing new graph descriptors for organic compds. was stimulated in recent years by their use in virtual screening of combinatorial libraries, database mining, similarity and diversity assessment. Recently, we have extended topol. indexes by defining a series of mol. graph operators, providing an effective systematization and generalization of these structural descriptors. A graph operator uses a math. equation to compute a family of related mol. graph descriptors with different mol. matrixes and various sets of parameters for atoms and bonds. In this paper we use structural descriptors computed with mol. graph operators to develop quant. structure-activity relationships (QSAR) models for the dihydrofolate reductase inhibition with diaminopyrimidines. The mol. descriptors are derived from five mol. matrixes, namely adjacency A, distance D, reciprocal distance RD, distance-path Dp, and reciprocal distance-path RDp. The QSAR models are obtained by selecting descriptors with a genetic algorithm, and the best models are validated with the leave-one-out cross-validation method. The QSAR models with the highest prediction power are comparable with those obtained with substituent consts. and neural networks, but they use a much lower number of parameters.

IT **73090-70-7**
RL: PRP (Properties)
(QSAR for dihydrofolate reductase inhibitors with mol. graph structural descriptors)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



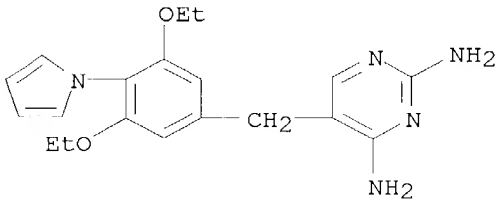
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:86403 CAPLUS

DOCUMENT NUMBER: 137:234
TITLE: In vivo activity of epiroprim, a dihydrofolate reductase inhibitor, singly and in combination with dapsone, against Mycobacterium leprae
AUTHOR(S): Dhople, Arvind M.
CORPORATE SOURCE: Department of Biological Sciences, Infectious Diseases Laboratory, Florida Institute of Technology, Melbourne, FL, 32901-6975, USA
SOURCE: International Journal of Antimicrobial Agents (2002), 19(1), 71-74
CODEN: IAAGEA; ISSN: 0924-8579
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antimicrobial effects of a new dihydrofolate reductase inhibitor, epiroprim, either singly or in combination with dapsone against Mycobacterium leprae, were evaluated in vivo using a mouse footpad model. When fed to mice at concentration of 0.05% in diet, epiroprim completely inhibited the growth of both dapsone-sensitive and dapsone-resistant strains of M. leprae in the footpads of mice and the effects were bactericidal. To achieve similar effects, the concentration of dapsone in the diet had to be 0.0005 and 0.01%, resp. When used in combination, the concns. of the drugs in the diet could be lowered by 50-80% and still achieve bactericidal effects. The data support the earlier results on in vitro studies and suggest the use of epiroprim in the multidrug regimen in the treatment of leprosy.

IT **73090-70-7**, Epiroprim
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epiroprim, singly and in combination with dapsone, against Mycobacterium leprae)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:67824 CAPLUS
DOCUMENT NUMBER: 136:363218
TITLE: Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution
AUTHOR(S): Poulin, Patrick; Theil, Frank-Peter
CORPORATE SOURCE: Non-Clinical Development-Drug Safety: Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(1),

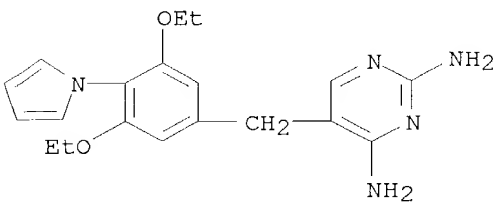
129-156
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In drug discovery and nonclin. development the volume of distribution at steady state (Vss) of each novel drug candidate is commonly determined under in vivo conditions. Therefore, it is of interest to predict Vss without conducting in vivo studies. The traditional description of Vss corresponds to the sum of the products of each tissue:plasma partition coefficient (Pt:p) and the resp. tissue volume in addition to the plasma volume Because data on vols. of tissues and plasma are available in the literature for mammals, the other input parameters needed to estimate Vss are the Pt:p's, which can potentially be predicted with established tissue composition-based equations. In vitro data on drug lipophilicity and plasma protein binding are the input parameters used in these equations. Such a mechanism-based approach would be particularly useful to provide first-cut ests. of Vss prior to any in vivo studies and to explore potential unexpected deviations between sets of predicted and in vivo Vss data, when the in vivo data become available during the drug development process. The objective of the present study was to use tissue composition-based equations to predict rat and human Vss prior to in vivo studies for 123 structurally unrelated compds. (acids, bases, and neutrals). The predicted data were compared with in vivo data obtained from the literature or at Roche. Overall, the average ratio of predicted-to-exptl. rat and human Vss values was 1.06 (SD=0.817, r=0.78, n=147). In fact, 80% of all predicted values were within a factor of two of the corresponding exptl. values. The drugs can therefore be separated into two groups. The first group contains 98 drugs for which the predicted Vss were within a factor of two of those exptl. determined (average ratio of 1.01, SD=0.39, r=0.93, n=118), and the second group includes 25 other drugs for which the predicted and exptl. Vss differ by a factor larger than two (average ratio of 1.32, SD=1.74, r=0.42, n=29). Thus, addnl. relevant distribution processes were neglected in predicting Vss of drugs of the second group. This was true especially in the case of some cationic-amphiphilic bases. The present study is the first attempt to develop and validate a mechanistic distribution model for predicting rat and human Vss of drugs prior to in vivo studies.

IT **73090-70-7**, Epiroprim
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(mechanism-based prediction of volume of distribution of drugs)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 208 THERE ARE 208 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:545723 CAPLUS
DOCUMENT NUMBER: 135:142230
TITLE: High purity lipopeptides, lipopeptide micelles and processes for preparing same
INVENTOR(S): Kelleher, Thomas J.; Lai, Jan-ji; Decourcey, Joseph P.; Lynch, Paul D.; Zenoni, Maurizio; Tagliani, Auro R.
PATENT ASSIGNEE(S): Cubist Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053330	A2	20010726	WO 2001-US1748	20010118
WO 2001053330	A3	20020418		
WO 2001053330	C2	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6696412	B1	20040224	US 2000-735191	20001128
BR 2001007731	A	20021001	BR 2001-7731	20010118
EP 1252179	A2	20021030	EP 2001-903121	20010118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003520807	T2	20030708	JP 2001-553802	20010118
NO 2002003476	A	20020920	NO 2002-3476	20020719

PRIORITY APPLN. INFO.:

US 2000-177170P	P	20000120
US 2000-735191	A	20001128
WO 2001-US1748	W	20010118

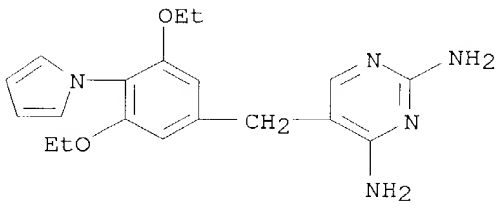
AB The invention discloses highly purified daptomycin and to pharmaceutical compns. comprising this compound The invention discloses a method of purifying daptomycin comprising the sequential steps of anion exchange chromatog., hydrophobic interaction chromatog. and anion exchange chromatog. The invention also discloses a method of purifying daptomycin by modified buffer enhanced anion exchange chromatog. An improved method for producing daptomycin by fermentation of Streptomyces roseosporus is described. The invention also discloses HPLC methods for anal. of daptomycin purity. Methods of using lipopeptide micelles for purifying lipopeptide antibiotics, such as daptomycin, and using them therapeutically are disclosed. Thus, daptomycin was produced in a fermentation culture of S. roseosporus and partially purified daptomycin (9.9 Kg) was purified by microfiltration from 5500 L of fermentation broth. The partially purified daptomycin was further purified and resulted in a bulk daptomycin preparation with a purity of 91%. The daptomycin preparation contained 14 impurities as determined by HPLC anal. The daptomycin preparation was applied to a Poros P150 anion exchange resin (PE Biosystems) in Tris buffer pH 7.0 containing 6M urea and allowed to bind to the resin. The resin was washed

with 3 column vols. of buffer prior to initiation of a NaCl gradient in the same buffer. Alternatively, the contaminants can be effectively removed from the column with a fixed salt level of 30 mM NaCl. The elution of purified daptomycin from the resin occurred at approx. 300 mM NaCl during a 0 to 1000 mM NaCl gradient. Daptomycin eluted from the column was greater than 99% pure as measured by the "first" HPLC method. The purified daptomycin contained only one detectable daptomycin contaminant. Anhydrodaptomycin and B-isomer were undetectable (<0.01% contamination). The level of the unidentified contaminant was 0.1-0.5%.

IT **73090-70-7**, Epiroprim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(purification of lipopeptides and lipopeptide micelles)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:527864 CAPLUS

DOCUMENT NUMBER: 135:251428

TITLE: Adaptive Neuro-Fuzzy Inference System: An Instant and Architecture-Free Predictor for Improved QSAR Studies

AUTHOR(S): Loukas, Yannis L.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry School of Pharmacy, University of Athens, Panepistimiopolis, Zografou, Athens, 157 71, Greece

SOURCE: Journal of Medicinal Chemistry (2001), 44(17), 2772-2783
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The application of an adaptive neuro-fuzzy inference system (ANFIS) has been developed for obtaining sufficient quant. structure-activity relationships (QSAR) with high accuracy. To this end, a data set of 68 pyrimidines derivs. as DHFR inhibitors, described first in the excellent independent studies of Hansch et al., was examined The ANFIS system, first time applied in the literature to QSAR studies, was trained using a hybrid algorithm consisting of back-propagation and least-squares estimation while the optimum number and shape of membership functions were obtained through the subtractive clustering algorithm. Prior to the development and evaluation of the ANFIS system, geometry optimization of the examined compds. was performed, deriving a series of diverse descriptors from which the best subset was selected by using a hybrid genetic algorithm system. The predictive abilities of the resulting models compared to those produced from classical multivariate regression such as linear and nonlinear (quadratic) partial least squares regression (PLS and QPLS, resp.). The ANFIS method outperformed both the PLS models as well as the published results, leading to substantial gain in both the prediction ability and

the computation speed (almost instant training).

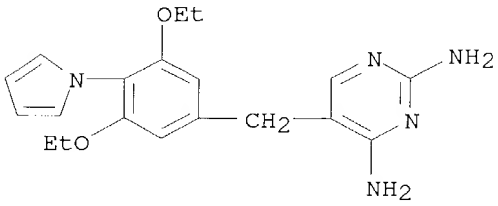
IT **73090-70-7**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adaptive neuro-fuzzy inference system: instant and architecture-free predictor for improved QSAR studies)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:453092 CAPLUS

DOCUMENT NUMBER: 135:61555

TITLE: Preparation of lipopeptides as antibacterial agents

INVENTOR(S): Hill, Jason; Parr, Ian; Morytko, Michael; Siedlecki, Jim; Yu, Xiang Yang; Silverman, Jared; Keith, Dennis; Finn, John; Christensen, Dale; Lazarova, Tsvetelina; Watson, Alan D.; Zhang, Yan

PATENT ASSIGNEE(S): Cubist Pharmaceuticals, Inc., USA; et al.

SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044274	A1	20010621	WO 2000-US34205	20001215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000016467	A	20020827	BR 2000-16467	20001215
EP 1246838	A1	20021009	EP 2000-991867	20001215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003517480	T2	20030527	JP 2001-544763	20001215
NO 2002002887	A	20020812	NO 2002-2887	20020617

PRIORITY APPLN. INFO.: US 1999-170946P P 19991215

US 2000-208222P P 20000530
WO 2000-US34205 W 20001215

OTHER SOURCE(S): MARPAT 135:61555
GI

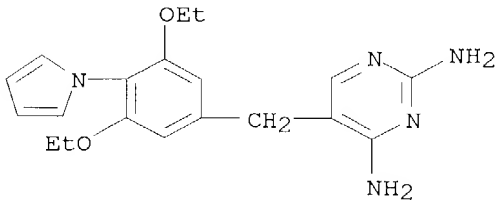
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Lipopeptides I [R is -N(B)(X)n-A; B is X''RY, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; RY is hydrido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or hydroxyl; X, X'' are C:O, C:S, C:NH, C:NRX, S:O or SO2; n is 0 or 1; RX is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, hydroxyl, alkoxy, carboxy or carboalkoxy; A is H, NH2, NHRA, NRARB, heteroaryl, cycloalkyl, heterocyclyl (RA, RB are alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or carboalkoxy) or when n is 0, then A is P(O)(OR50)OR51, P(O)R52R53, or P(O)(OR50)R53, where R50-R53 are alkyl; alternatively B and A may form a 5-7 membered heterocyclic or heteroaryl ring; R1 is defined similarly to R (with provisos); R2 is CH2CR17R18-ring, where R17 and R18 are hydrido, halo, hydroxyl, alkoxy, amino, thio, sulfinyl, sulfonyl, etc. or CR17R18 are CO, C(:S), oxime or hydrazone group] were prepared for use as antibacterials. Thus, treating daptomycin with 4-fluorobenzaldehyde and sodium triacetoxyborohydride in dry DMF for 24 h afforded I [R = NHCO(CH2)8Me, R1 = NHCH2C6H4F-4, R2 = CH2COC6H4NH2-o], which showed MIC (S. Aureus) ≤ 1 μg/mL.

IT **73090-70-7**, Epiroprim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of lipopeptides as antibacterial agents)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:453090 CAPLUS
DOCUMENT NUMBER: 135:61554
TITLE: Preparation of novel lipopeptides as antibacterial agents
INVENTOR(S): Hill, Jason; Parr, Ian; Morytko, Michael; Siedlecki, Jim; Yu, Xiang Yang; Silverman, Jared; Keith, Dennis; Finn, John; Christensen, Dale; Lazarova, Tsvetelina; Watson, Alan D.; Zhang, Yan
PATENT ASSIGNEE(S): Cubist Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044272	A2	20010621	WO 2000-US34118	20001215
WO 2001044272	A3	20011129		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002025924	A1	20020228	US 2000-738742	20001215
EP 1240181	A2	20020918	EP 2000-986444	20001215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000017026	A	20030107	BR 2000-17026	20001215
JP 2003517004	T2	20030520	JP 2001-544761	20001215
NO 2002002888	A	20020802	NO 2002-2888	20020617

PRIORITY APPLN. INFO.: US 1999-170943P P 19991215
WO 2000-US34118 W 20001215

OTHER SOURCE(S): MARPAT 135:61554
GI

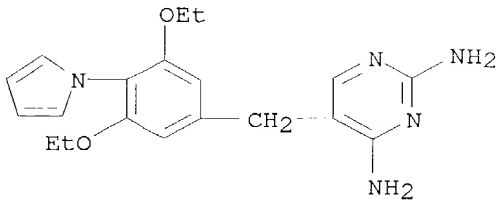
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Lipopeptides I [R is -N(B)(X)n-A; B is X''RY, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; RY is hydrido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or hydroxyl; X, X'' are C:O, C:S, C:NH, C:NRX, S:O or SO2; n is 0 or 1; RX is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, hydroxyl, alkoxy, carboxy or carboalkoxy; A is H, NH2, NHRA, NRARB, heteroaryl, cycloalkyl, heterocyclyl (RA, RB are alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or carboalkoxy) or when n is 0, then A is P(O)(OR50)OR51, P(O)R52R53, or P(O)(OR50)R53, where R50-R53 are alkyl (with provisos); R1 is defined similarly to R; R2 is CH2CR17R18-ring, where R17 and R18 are hydrido, halo, hydroxyl, alkoxy, amino, thio, sulfinyl, sulfonyl, etc. or CR17R18 are CO, C(:S), oxime or hydrazone group] were prepared for use as antibacterials. Thus, daptomycin was Boc-protected, deacylated using deacylase enzyme, and reacted with octyl isocyanate to give I [R = NHCONH(CH2)7Me, R1 = NH2, R2 = CH2COC6H4NH2-o], which showed MIC (S. Aureus) > 1 ≤ 10 μg/mL mg/kg.

IT **73090-70-7**, Epiroprim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of novel lipopeptides as antibacterial agents)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:453089 CAPLUS
DOCUMENT NUMBER: 135:61553
TITLE: Preparation of novel lipopeptides as antibacterial agents
INVENTOR(S): Hill, Jason; Parr, Ian; Morytko, Michael; Siedlecki, Jim; Yu, Xiang Yang; Silverman, Jared; Keith, Dennis; Finn, John; Christensen, Dale; Lazarova, Tsvetelina; Watson, Alan D.; Zhang, Yan
PATENT ASSIGNEE(S): Cubist Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044271	A2	20010621	WO 2000-US34051	20001215
WO 2001044271	A3	20020307		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002058785	A1	20020516	US 2000-739535	20001215
EP 1240182	A2	20020918	EP 2000-991409	20001215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000017028	A	20030107	BR 2000-17028	20001215
JP 2003517003	T2	20030520	JP 2001-544760	20001215
NO 2002002886	A	20020802	NO 2002-2886	20020617

PRIORITY APPLN. INFO.: US 1999-170945P P 19991215
WO 2000-US34051 W 20001215

OTHER SOURCE(S): MARPAT 135:61553
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

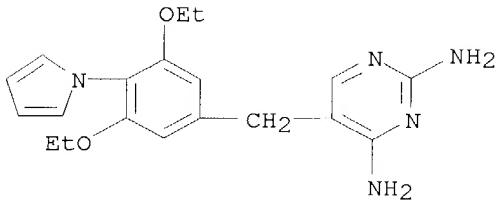
AB Lipopeptides I [R and R1 are -N(B)(X)n-A; B is X'RY, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; RY is hydrido,

alkyl, alkenyl, alkynyl, aryl,heteroaryl, cycloalkyl, heterocyclyl or hydroxyl; X, X' are C:O, C:S, C:NH, C:NRX, S:O or SO2; n is 0 or 1; RX is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, hydroxyl, alkoxy, carboxy or carboalkoxy; A is H, NH2, NHRA, NRARB, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, aryl, heteroaryl, cycloalkyl, heterocyclyl (RA, RB are alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or carboalkoxy) or when n is 0, then A is P(O)(OR50)OR51, P(O)R52R53, or P(O)(OR50)R53, where R50-R53 are alkyl; alternatively, B and A together form a 5-7 membered heterocyclic or heteroaryl ring; R2 is CH2CR17R18-ring, where R17 and R18 are hydrido, halo, hydroxyl, alkoxy, amino, thio, sulfinyl, sulfonyl, etc. or CR17R18 are CO, C(:S), oxime or hydrazone group] were prepared for use as antibacterials. Thus, sulfamic acid (89.9 mg) and sodium nitrite (51.1 mg) were added to a solution of daptomycin (1 g) in 0.1 M HCl (31 mL) at 0°. Aqueous potassium O-ethylxanthic acid (497 mg) was added and the mixture was heated at 60° for 1 h to afford I [R = NHCO(CH2)8Me, R1 = NH2, R2 = CH2CO-o-C6H4SC(S)OEt], which showed MIC (S. Aureus and E. faecalis) and ED50 > 1 ≤ 10 μg/mL or mg/kg, resp.

IT **73090-70-7**, Epiroprim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of novel lipopeptides as antibacterial agents)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:338504 CAPLUS
DOCUMENT NUMBER: 134:340518
TITLE: Substituted 5-benzyl-2,4-diaminopyrimidines
INVENTOR(S): Guerry, Philippe; Mohr, Peter; Muller, Marc; Mueller, Werner; Pflieger, Philippe
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 177 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

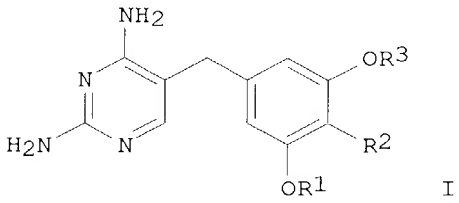
applicants

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032633	A1	20010510	WO 2000-CH575	20001027

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1230224 A1 20020814 EP 2000-969149 20001027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003516320 T2 20030513 JP 2001-534784 20001027
PRIORITY APPLN. INFO.: CH 1999-2021 A 19991104
WO 2000-CH575 W 20001027
OTHER SOURCE(S): MARPAT 134:340518

GI



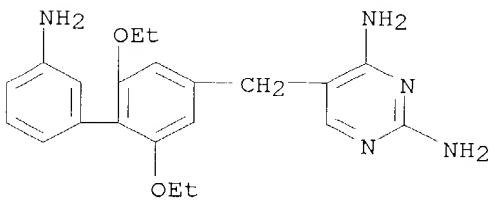
I

AB Substituted 5-benzyl-2,4-diaminopyrimidines I [R1 = C2-C3 alkyl; R2 = (un)substituted heterocyclyl, Ph, naphthyl; R3 = (un)substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, alkylsulfonyl, cycloalkylsulfonyl, cycloalkylalkylsulfamoyl, heterocyclylsulfonyl, heterocyclylalkylsulfonyl, dialkylsulfamoyl] were prepared for use as antibacterial agents. Thus, I [R1 = R3 = Et, R2 = I] was prepared from 3,5-(HO)2C6H3CO2H by iodination, esterification, etherification, reduction to 4,3,5-I(EtO)2C6H2CHO via 4,3,5-I(EtO)2C6H2CH2OH, reaction with PhNHCH2CH2CN, and cyclization with guanidine-HCl. I [R1 = R3 = Et, R2 = I] was coupled with 3-H2NC6H4B(OH)2 to give I [R1 = R3 = Et, R2 = 3-H2NC6H4] which had an IC50 against dihydrofolate reductase from Streptococcus pneumoniae 1/1 of 0.19 μM.

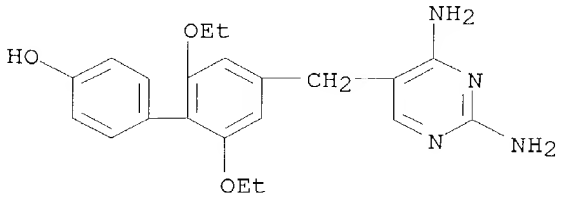
IT **338454-08-3P 338454-33-4P 338454-81-2P**
338455-03-1P 338455-06-4P 338455-11-1P
338455-35-9P 338455-39-3P 338455-48-4P
338455-71-3P 338455-73-5P 338455-77-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of substituted 5-benzyl-2,4-diaminopyrimidines as bacterial dihydrofolate reductase inhibitors)

RN 338454-08-3 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(3'-amino-2,6-diethoxy[1,1'-biphenyl]-4-yl)methyl]- (9CI) (CA INDEX NAME)



RN 338454-33-4 CAPLUS
CN [1,1'-Biphenyl]-4-ol, 4'-[(2,4-diamino-5-pyrimidinyl)methyl]-2',6'-diethoxy- (9CI) (CA INDEX NAME)



RN 338454-81-2 CAPLUS
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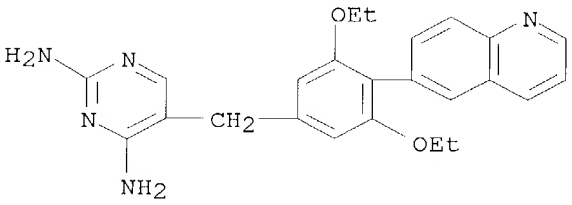

RN 338455-03-1 CAPLUS
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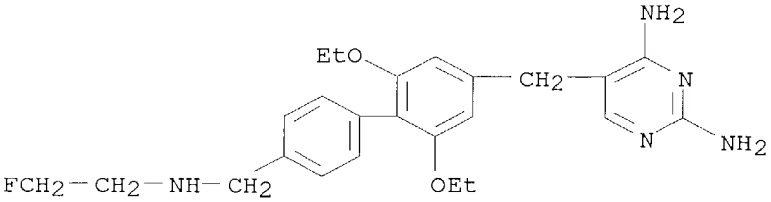

RN 338455-06-4 CAPLUS
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study); PREP (Preparation); USES (Uses)
(preparation of substituted 5-benzyl-2,4-diaminopyrimidines as bacterial dihydrofolate reductase inhibitors)

RN 338454-09-4 CAPLUS
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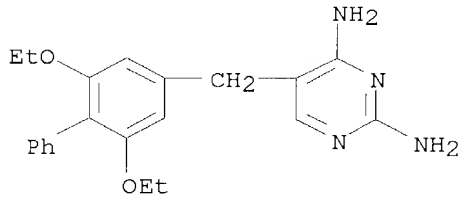

RN 338454-10-7 CAPLUS
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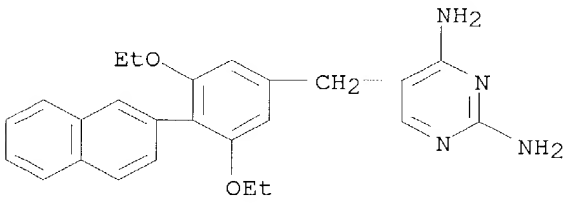
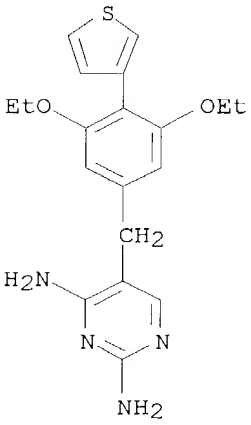


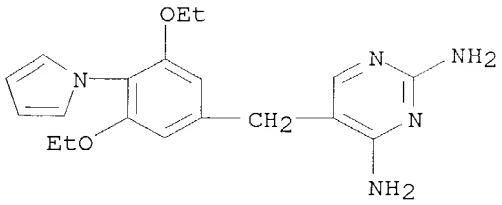
RN 338454-21-0 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(3-thienyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:282455 CAPLUS
DOCUMENT NUMBER: 135:116488
TITLE: Prediction of adipose tissue:plasma partition coefficients for structurally unrelated drugs
AUTHOR(S): Poulin, Patrick; Schoenlein, Kerstin; Theil, Frank-Peter
CORPORATE SOURCE: Pharmaceuticals Division, Non-Clinical Development-Drug Safety, F. Hoffmann-La Roche, Ltd., Basel, CH-4070, Switz.
SOURCE: Journal of Pharmaceutical Sciences (2001), 90(4), 436-447
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tissue:plasma (Pt:p) partition coeffs. (PCs) are important parameters describing tissue distribution of drugs. The ultimate goal in early drug discovery is to develop and validate in silico methods for predicting a priori the Pt:p for each new drug candidate. In this context, tissue composition-based equations have recently been developed and validated for predicting a priori the non-adipose and adipose Pt:p for neutral organic solvents and pollutants. For ionizable drugs that bind to different degrees to common plasma proteins, only their non-adipose Pt:p values have been predicted with these equations. The only compound-dependent input parameters for these equations are the lipophilicity parameter, such as olive oil-water PC (Kvo:w) or n-octanol-water PC (Po:w), and/or unbound fraction in plasma (fup) determined under in vitro conditions. Tissue composition-based equations could potentially also be used to predict adipose tissue-plasma PCs (Pat:p) for ionized drugs. The main objective of the present study was to modify these equations for predicting in vivo Pat:p (white fat) for 14 structurally unrelated ionized drugs that bind substantially to plasma macromols. in rats, rabbits, or humans. The second objective was to verify whether Kvo:w or Po:w provides more accurate predictions of in vivo Pat:p (i.e., to verify whether olive oil or n-octanol is the better surrogate for lipids in adipose tissue). The second objective was supported by comparing in vitro data on Pat:p with those on olive oil-plasma PC (Kvo:p) for five drugs. Furthermore, in vivo Pat:p was not only predicted from Kvo:w and Po:w of the non-ionized species, but also from Kvo:w* and Po:w*, taking into account the ionized species in addition The Pat:p predicted from Kvo:w*, Po:w*, and Po:w differ from the in vivo Pat:p by an average factor of 1.17 (SD = 0.44, r = 0.95), 15.0 (SD = 15.7, r = 0.59), and 40.7 (SD = 57.2, r = 0.33), resp. The in vitro values of Kvo:p differ from those of Pat:p by an average factor of 0.86 (SD = 0.16, r = 0.99, n = 5). The results demonstrate that (i) the equation using only data on fup as input and olive oil as lipophilicity surrogate is able to provide accurate predictions of in vivo Pat:p, and (ii) olive oil is a better surrogate of the adipose tissue lipids than n-octanol. The present study is an innovative method for predicting in vivo fat partitioning of drugs in mammals.
IT **73090-70-7**, Epiroprim
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prediction of adipose tissue-plasma partition coeffs. for structurally unrelated drugs)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)

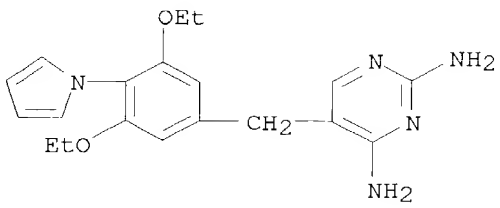


REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:169850 CAPLUS
DOCUMENT NUMBER: 134:338138
TITLE: Experimental in vitro efficacy study on the interaction of epiroprim plus isoniazid against Mycobacterium tuberculosis
AUTHOR(S): Dosso, Mireille; Ouattara, Lassina; Cherif, Abdou Magid; Bouzid, Samir Amor; Haller, Louis; Fernex, Michel
CORPORATE SOURCE: Institut Pasteur de Cote d'lvoire, Abidjan, 01, Cote d'Ivoire
SOURCE: Chemotherapy (Basel, Switzerland) (2001), 47(2), 123-127
CODEN: CHTHBK; ISSN: 0009-3157
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thirty Mycobacterium tuberculosis strains (8: INHR/INHR, 12: INHR/RIFS, 10: INHS/RIFS) were examined against MICs of epiroprim (EPM) and isoniazid (INH) sep. or in association EPM alone proved to be insufficiently active against the various mycobacterial isolates (MIC ≥256 μg/mL).
The observed average sensitivity to the association of EPM plus INH was, in contrast, considerably increased, as reflected by reduced MICs and lower percentages of resistant strains. MICs ranged between 16 and 32 μg/mL EPM and 2 and 4 μg/mL INH for INHR strains. All INHS isolates were inhibited by a concentration of 0.125 μg/mL EPM and 0.06 μg/mL INH. The fractional inhibitory concentration indexes indicated an additive activity on INHR/RIFR strains and a synergistic activity on INHR/RIFS and INHS/RIFS strains. The synergistic activity of this drug association needs to be confirmed in an animal model.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro efficacy of epiroprim and isoniazid alone or combined against Mycobacterium tuberculosis phenotypes)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



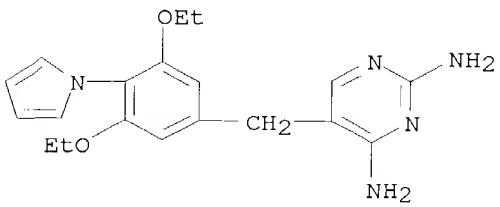
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:114257 CAPLUS
DOCUMENT NUMBER: 134:277817
TITLE: Antimicrobial activities of dihydrofolate reductase inhibitors, used singly or in combination with dapsone, against Mycobacterium ulcerans
AUTHOR(S): Dhople, Arvind M.
CORPORATE SOURCE: Department of Biological Sciences, Florida Institute of Technology, Melbourne, FL, 32901, USA
SOURCE: Journal of Antimicrobial Chemotherapy (2001), 47(1), 93-96
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Development of new treatments against Mycobacterium ulcerans infection has become crucial because of its wide-scale prevalence throughout the world. The effects of dihydrofolate reductase inhibitors, used either singly or in combination with dapsone against M. ulcerans were evaluated in vitro. When used singly, epiroprim was the most potent, with MICs between 0.5 and 1.0 mg/L, while trimethoprim was totally ineffective. The MICs of K-130 and brodimoprim ranged from 1.0-2.0 mg/L for the former to 2.0-16.0 mg/L for the latter. When combined with dapsone, synergic effects were observed with epiroprim. These results indicate the great potential of epiroprim in treating M. ulcerans infections.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antimicrobial activities of dihydrofolate reductase inhibitors alone or combined with dapsone against Mycobacterium ulcerans)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:842012 CAPLUS
DOCUMENT NUMBER: 134:16544
TITLE: Medicinal compositions containing anti-Fas antibody
INVENTOR(S): Serizawa, Nobufusa; Ichikawa, Kimihisa; Yoshida, Hiroko
PATENT ASSIGNEE(S): Sankyo Company, Ltd., Japan
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

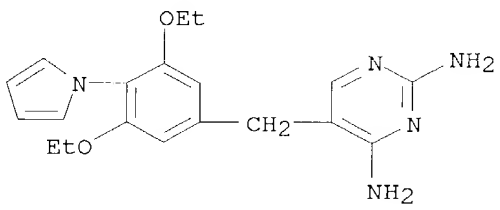
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071160	A1	20001130	WO 2000-JP3324	20000524
W: AU, BR, CA, CN, CZ, HU, ID, IL, IN, KR, MX, NO, NZ, PL, RU, TR, US, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2001039892	A2	20010213	JP 2000-152283	20000524
BR 2000010909	A	20020219	BR 2000-10909	20000524
EP 1180369	A1	20020220	EP 2000-931546	20000524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 761544	B2	20030605	AU 2000-49486	20000524
RU 2222347	C2	20040127	RU 2001-131725	20000524
US 2002103212	A1	20020801	US 2001-989620	20011120
ZA 2001009575	A	20030220	ZA 2001-9575	20011120
NO 2001005711	A	20020111	NO 2001-5711	20011123

PRIORITY APPLN. INFO.: JP 1999-143033 A 19990524
WO 2000-JP3324 W 20000524

AB Novel medicinal compns. containing anti-Fas antibody which are useful as preventives or remedies for autoimmune diseases or rheumatoid arthritis. More particularly, medicinal compns. containing as the active ingredients anti-human Fas antibody having an activity of inducing apoptosis and a compound having an antagonism to folic acid or an effect of inhibiting dihydrofolate reductase. By using these medicinal compns., the content of anti-Fas antibody can be reduced in preventives or remedies for autoimmune diseases or rheumatoid arthritis containing anti-Fas antibody. Thus, the possibility of the appearance of the tolerance in the patient's body due to the expression of an antibody against the anti-Fas antibody, etc., which makes it possible to provide excellent preventives or remedies usable in long-term administration.

IT **73090-70-7**, Epiroprim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing anti-Fas antibody and folic acid antagonist or dihydrofolate reductase inhibitors for treatment of autoimmune disease or rheumatoid arthritis)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)

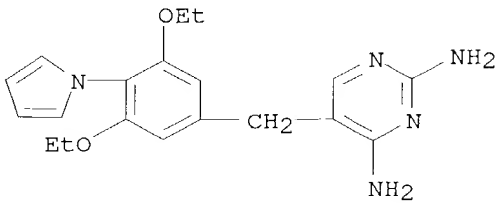


REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:492518 CAPLUS
DOCUMENT NUMBER: 134:25104
TITLE: Interaction energy analysis of nonclassical antifolates with human dihydrofolate reductase
AUTHOR(S): Pitts, Conrad; Bowen, Donnell; Southerland, William M.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Howard University College of Medicine, Washington, DC, 20059, USA
SOURCE: Journal of Molecular Modeling [online computer file] (2000), 6(6), 467-476
CODEN: JMMOFK; ISSN: 0948-5023
URL: http://link.springer.de/link/service/journals/00894/papers/0006006/00060467.pdf
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The x-ray structure of the PTX:NADPH:L22F human mutant DHFR ternary complex was used as a structural template to generate structural models for the following wild type DHFR complexes: PTX:DHFR:NADPH, TMP:DHFR:NADPH, EPM:DHFR:NADPH, and TMQ:DHFR:NADPH. Each of these complexes were subsequently modeled in a 60 Å cube of explicit water and minimized to a rms gradient of from 1.0-3.0.10-5 kcal.Å-1. For each complex, interaction energies were calculated for the antifolate interaction with each of the following: the DHFR binding site residues, the entire DHFR protein, the solvated complex (containing DHFR, NADPH, and solvent water), water alone, and NADPH. Addnl., each antifolate was subdivided into distinct substructural regions and interaction energy calcns. were performed in order to evaluate their contributions to overall antifolate interaction. Each antifolate showed its most stable interaction with the solvated complex. Substructural regions which consisted of a nitrogen containing aromatic ring system contributed most to the stability of the antifolate interactions, while the hydrocarbon aromatic rings, methoxy, and ethoxy groups showed much less stable interaction energies. Since the different substructural regions of nonclassical antifolates differ in their contributions to overall antifolate binding, those substructural regions which exhibit relatively unfavorable interaction energies may constitute important targets in the design of improved DHFR inhibitors.

IT **73090-70-7D**, Epiroprim, complexes with dihydrofolate reductase and NADPH
RL: PRP (Properties)
(interaction energy anal. of nonclassical antifolates with human dihydrofolate reductase)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



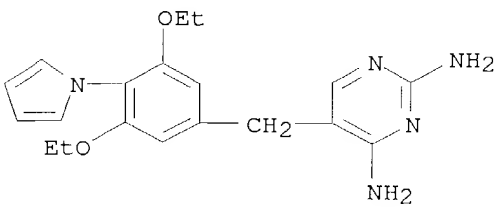
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:561112 CAPLUS
DOCUMENT NUMBER: 131:308763
TITLE: In vitro activity of epiroprim, a dihydrofolate reductase inhibitor, singly and in combination with brodimoprim and dapsone, against Mycobacterium leprae
AUTHOR(S): Dhople, A. M.
CORPORATE SOURCE: Department of Biological Sciences, Florida Institute of Technology, Melbourne, FL, USA
SOURCE: International Journal of Antimicrobial Agents (1999), 12(4), 319-323
CODEN: IAAGEA; ISSN: 0924-8579
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antimicrobial effects of a new dihydrofolate reductase inhibitor, epiroprim, alone and in combination with dapsone and brodimoprim against Mycobacterium leprae were evaluated in vitro in cell-free culture system. Two biochem. parameters were used to measure metabolic activity (and growth) of the organism. The minimal inhibitory activity of epiroprim against M. leprae was 10 mg/l and the action was bactericidal. When combined with dapsone, epiroprim exhibited a strong synergism; on the other hand, combination of epiroprim and brodimoprim provided only additive effects. The results suggest that epiroprim can be a component in multidrug therapy regimen in leprosy.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(activity of epiroprim as dihydrofolate reductase inhibitor singly and in combination with brodimoprim and dapsone against Mycobacterium leprae)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



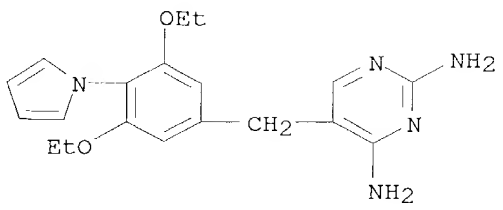
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:548446 CAPLUS
DOCUMENT NUMBER: 131:295113
TITLE: Inhibition of dihydrofolate reductases from Toxoplasma gondii, Pneumocystis carinii, and rat liver by rotationally restricted analogues of pyrimethamine and metoprine
AUTHOR(S): Rosowsky, Andre; Queener, Sherry F.; Cody, Vivian
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute and Departments of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Drug Design and Discovery (1999), 16(1), 25-40
CODEN: DDDIEV; ISSN: 1055-9612
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Twenty-one conformationally restricted tricyclic pyrimethamine and metoprine analogs with one or two chlorine atoms, or other substituents, at different positions of the Ph ring were tested for potency and species selectivity against dihydrofolate reductase (DHFR) from Toxoplasma gondii, Pneumocystis carinii, and rat liver. Heterocyclic systems studied included indeno[2,1-d]pyrimidines, benzo[f]quinazolines, and benzo[3,4]cyclohepta[1,2-d]pyrimidines. All but one of the analogs were more potent against T. gondii and rat liver DHFR than against P. carinii DHFR, and those with a one-carbon (CH2) bridge were generally less potent than those with a two-carbon (CH2CH2, CH=CH) or three-carbon (CH2CH2CH2) bridge. Although a number of compds. with a two- and three-carbon bridge were more potent than pyrimethamine against P. carinii DHFR, and especially T. gondii DHFR, none of them were selective for the P. carinii vs. the mammalian enzyme, and only those with a one-carbon bridge showed selectivity approaching that of pyrimethamine for the T. gondii enzyme. Computer-simulated docking into the active site pocket of P. carinii and human DHFR suggested that, as a group, the rotationally restricted tricyclic structures are at a disadvantage relative to pyrimethamine and metoprine, in that torsional relief of unfavorable steric interactions between the chlorine atoms and two critical serine and threonine residues in the active site is prevented by the bridge.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of dihydrofolate reductases from Toxoplasma gondii, Pneumocystis carinii, and liver by rotationally restricted analogs of pyrimethamine and metoprine)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)

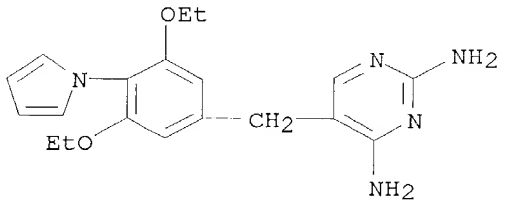


REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:98548 CAPLUS
DOCUMENT NUMBER: 126:207158
TITLE: A cytotoxicity assay for evaluation of candidate anti-Pneumocystis carinii agents
AUTHOR(S): Cushion, Melanie T.; Chen, Franklin; Kloepfer, Natalie
CORPORATE SOURCE: Dep. Internal Med., Univ. Cincinnati Coll. Med., Cincinnati, OH, 45627-0560, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1997), 41(2), 379-384
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of over 60 agents representing several different classes of compds. were evaluated for their effects on the ATP pools of Pneumocystis carinii populations derived from immunosuppressed rats. A cytotoxicity assay based on an ATP-driven bioluminescent reaction was used to determine the concentration of agent which decreased the P. carinii ATP pools by 50% vs. untreated controls (IC50). A ranking system based on the IC50 values was devised for comparison of relative responses among the compds. evaluated in the cytotoxic assay and for comparison to in vivo efficacy. With few exceptions, there was a strong correlation between results from the ATP assay and the performance of the compound in vivo. Antibiotics, with the exception of trimethoprim-sulfamethoxazole (TMP-SMX), were ineffective at reducing the ATP pools and were not active, clin. or in the rat model of P. carinii pneumonia. Likewise, other agents not expected to be effective, e.g., antiviral compds., did not show activity. Standard anti-P. carinii compds., e.g., TMP-SMX, pentamidine, and dapsone, dramatically reduced ATP levels. Analogs of the quinone and topoisomerase inhibitor groups were shown to reduce ATP concns. and hold promise for further in vivo investigation. The cytotoxicity assay provides a rapid assessment of response, does not rely on replicating organisms, and should be useful for assessment of structure-function relationships.

IT **73090-70-7**, Ro 11-8958
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytotoxicity assay for evaluation of candidate anti-Pneumocystis carinii agents)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)

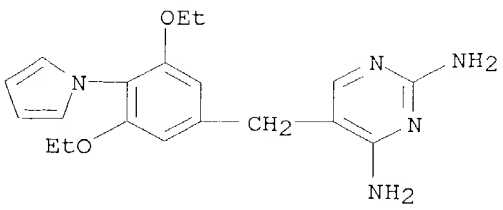


REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:98376 CAPLUS
DOCUMENT NUMBER: 126:194887
TITLE: Immunodeficient and immunosuppressed mice as model to test anti-Pneumocystis carinii drugs
AUTHOR(S): Walzer, Peter D.; Runck, Jennifer; Steele, Paul; White, Michael; Linke, Michael J.; Sidman, Charles L.
CORPORATE SOURCE: Res. Sci. Veterans Affairs Med. Cent., Univ. Cincinnati Coll. Med., Cincinnati, OH, 45267, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1997), 41(2), 251-258
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Congenitally immunodeficient and immunosuppressed normal mice with naturally acquired Pneumocystis carinii infection were compared as models for testing anti-P. carinii drugs. Among the immunodeficient mice, mice with severe combined immunodeficiency disease (scid), which lack B and T cells, had higher levels of P. carinii pneumonia than did μMT mice, which lack B cells. Normal mice administered dexamethasone in the drinking water had more extensive pneumocystosis than mice administered parenteral methylprednisolone or hybridoma cells making a monoclonal antibody to CD4 cells. The standard anti-P. carinii drugs trimethoprim (TMP)-sulfamethoxazole (SMX), pentamidine, and atovaquone, which work well in rats and humans, worked well in the mice. Clindamycin and primaquine were effective in the scid and μMT mice but not in the immunosuppressed normal mice. High doses of epiroprim, an analog of TMP, appeared to enhance the activities of low doses of SMX and dapsone, while high doses of TMP did not; however, further studies are needed before definitive conclusions about the actions of these drugs can be drawn. Taken together, the data obtained in this study support the growing body of literature suggesting that the mouse is a valid alternative to the rat as a model for testing anti-P. carinii drugs. Addnl. differences involving the activities of individual drugs in these models will probably emerge as more experience is gained.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of anti-Pneumocystis carinii drugs in immunodeficient and immunosuppressed mice)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



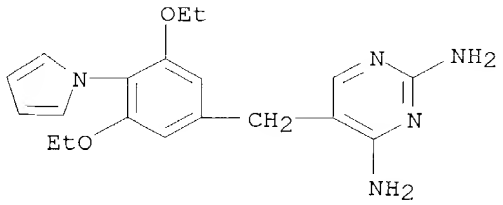
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:16568 CAPLUS
DOCUMENT NUMBER: 126:84010
TITLE: Simple HPLC determination of the concentrations of epiroprim in the serum and brains of mice
AUTHOR(S): Lee, How Sung; Change, Hernan R.; Khoo, Yok Moi
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, National University of Singapore, Singapore
SOURCE: Journal of Pharmacy and Pharmacology (1996), 48(10), 1090-1092
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epiroprim, an analog of trimethoprim, has been shown to potentiate the efficacy of dapsone in exptl. parasitic infections. A simple and accurate HPLC method has been developed to estimate epiroprim in serum and brain. Blood and brains from mice were sampled 0, 30, 75, 120 and 240 min after 50 or 100 mg kg-1 oral gavage. The drug and added internal standard metoprine in serum and brain supernatant were isolated by solid-phase extraction (Supelclean LC-SCX). The HPLC system consisted of a 150+4.6 mm Hypersil 5 μm ODS column. The mobile phases contained various proportions of acetonitrile, methanol and phosphate buffer (0.1 M). Peaks were detected by UV absorbance at 210 nm. Serum concns. of epiroprim were highest at 30 min for both 50 and 100 mg kg-1 doses, 173±20 and 207±25 ng mL-1, resp., falling to 8±5 and 18±6 ng mL-1, resp., at 240 min. Epiroprim concns. in the brain correlated well with those in the serum, with levels of 223±69 and 265±21 ng g-1 falling to 10±10 and 31±11 ng g-1, resp. Epiroprim is rapidly absorbed and distributed to the brain.

IT **73090-70-7**, Epiroprim
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(epiroprim concns. in serum and brains of mice by simple HPLC determination)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



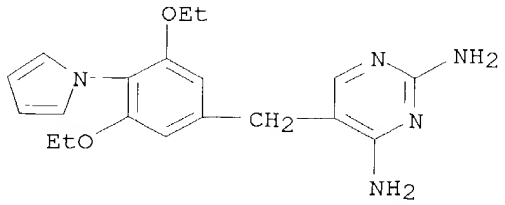
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:544237 CAPLUS
DOCUMENT NUMBER: 125:185018
TITLE: Combination of PS-15, epiroprim, or pyrimethamine with dapsone in prophylaxis of Toxoplasma gondii and Pneumocystis carinii dual infection in a rat model
AUTHOR(S): Brun-Pascaud, Monique; Chau, Francoise; Garry, Louis; Jacobus, David; Derouin, Francis; Girard, Pierre-Marie
CORPORATE SOURCE: Inst. National Sante Rech. Med. Unite 13, Hopital Bichat, Paris, Fr.
SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(9), 2067-2070
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

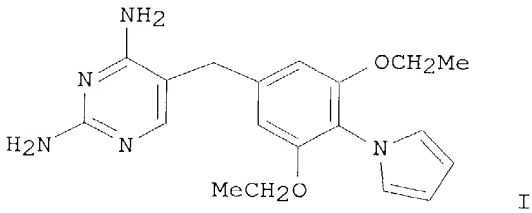
AB In a rat model of dual infection, the authors studied such dihydrofolate reductase (DHFR) inhibitors as PS-15 (25 mg/kg of body weight), epiroprim (100 mg/kg), and pyrimethamine (3 mg/kg) alone or in combination with various doses of dapsone (50, 25, or 5 mg/kg) for the prevention of pneumocystosis and toxoplasmosis. Rats latently infected with Pneumocystis carinii were immunosuppressed by corticosteroids for 7 wk, and the drugs were administered from the initiation of the corticosteroid treatment. At week 5, the rats were inoculated i.p. with the RH strain of Toxoplasma gondii. Infections were monitored by the counting of P. carinii cysts in lung homogenates and the titration of T. gondii in organs by quant. culture and an indirect immunofluorescence assay. Fourteen of the 15 untreated rats died after T. gondii challenge, with P. carinii infection in the lungs and T. gondii infection in the lungs, liver, spleen, and brain. Of the three tested DHFR inhibitors, only PS-15 exhibited anti-P. carinii activity; none prevented toxoplasmosis in 100% of the rats. After the DHFR inhibitors were combined with dapsone (50 or 25 mg/kg), both pneumocystosis and toxoplasmosis were completely prevented. On the basis of these results, PS-15 and epiroprim combined with dapsone are candidates for use for the prevention of both pneumocystosis and toxoplasmosis.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of PS-15, epiroprim, or pyrimethamine with dapsone in prophylaxis of Toxoplasma gondii and Pneumocystis carinii dual infection in a rat model)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:331556 CAPLUS
DOCUMENT NUMBER: 125:29877
TITLE: Antibacterial activities of epiroprim, a new dihydrofolate reductase inhibitor, alone and in combination with dapsone
AUTHOR(S): Locher, Hans H.; Schlunegger, Heidi; Hartman, Peter G.; Angehrn, Peter; Then, Rudolf L.
CORPORATE SOURCE: Preclinical Research, F. Hoffmann-La Roche Ltd., Basel, CH-4002, Switz.
SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(6), 1376-1381
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



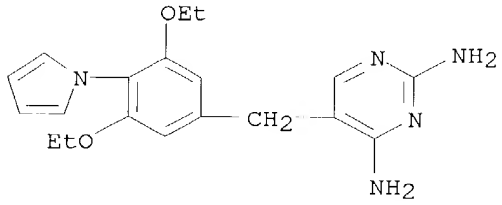
I

AB Epiroprim (Ro 11-8958, I) is a new selective inhibitor of microbial dihydrofolate reductase. I displayed excellent activity against staphylococci, enterococci, pneumococci, and streptococci which was considerably better than that of trimethoprim (TMP). I was also active against TMP-resistant strains, although the MICs were still relatively high. Its combination with dapsone (DDS) was synergistic and showed an in vitro activity superior to that of the TMP combination with sulfamethoxazole (SMZ). The I-DDS (ratio, 1:19) combination inhibited more than 90% of all important gram-pos. pathogens at a concentration of 2 + 38 μg/mL. Only a few highly TMP-resistant staphylococci and enterococci were not inhibited. I was also more active than TMP against Moraxella catarrhalis, Neisseria meningitidis, and Bacteroides spp., but it was less active than TMP against all other gram-neg. bacteria tested. Atypical mycobacteria were poorly susceptible to I, but the combination with DDS was synergistic and active at concns. most probably achievable in biol. fluids (MICs from 0.25 + 4.75 to 4 + 76 μg/mL). I and the I-DDS combination were also highly active against exptl. staphylococcal infections in a mouse septicemia model. The combination I-DDS has

previously been shown to exhibit activity in Pneumocystis carinii and Toxoplasma models and, as shown in the present study, also shows good activity against a broad range of bacteria, including many strains resistant to TMP and TMP-SMZ.

IT **73090-70-7**, Epiroprim **177744-95-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibacterial activities of epiroprim, a new dihydrofolate reductase inhibitor, alone and in combination with dapsone)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 177744-95-5 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]-, mixt. with 4,4'-sulfonylbis[benzenamine] (9CI) (CA INDEX NAME)

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CRN 73090-70-7
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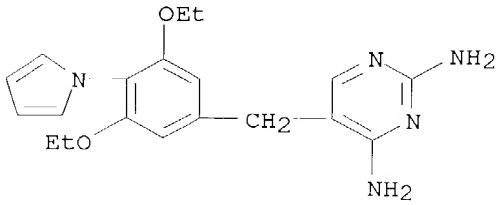
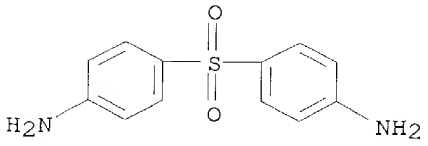


CM 2

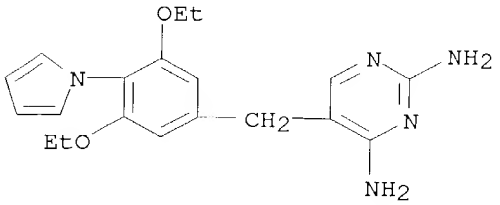
CRN 80-08-0
CMF C12 H12 N2 O2 S



L3 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:258089 CAPLUS
DOCUMENT NUMBER: 124:331872
TITLE: Efficacy of epiroprim (Roll-8958), a new dihydrofolate reductase inhibitor, in the treatment of acute Toxoplasma infection in mice
AUTHOR(S): Martinez, Anthony; Allegra, Carmen J.; Kovacs, Joseph A.
CORPORATE SOURCE: National Cancer Institute, National Institutes Health, Bethesda, MD, USA
SOURCE: American Journal of Tropical Medicine and Hygiene (1996), 54(3), 249-52
CODEN: AJTHAB; ISSN: 0002-9637
PUBLISHER: American Society of Tropical Medicine and Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Toxoplasma gondii is a major cause of focal encephalitis in patients with acquired immunodeficiency syndrome. Epiroprim, an inhibitor of dihydrofolate reductase, was evaluated in vitro and in a mouse model of acute infection for activity against T. gondii. The 50% inhibitory concentration (IC50) of epiroprim for T. gondii dihydrofolate reductase was 0.9 μM, similar to that of pyrimethamine, but epiroprim was 650-fold more selective than pyrimethamine for T. gondii compared with human dihydrofolate reductase. While i.p. administered epiroprim (300 mg/kg/day for 14 days) alone was ineffective in mice acutely infected with the RH strain of T. gondii, 100% survival was seen when it was combined with orally administered sulfadiazine (375 mg/kg/day), which alone was also ineffective. Increases in survival were seen in combination with doses of sulfadiazine as low as 0.375 mg/kg/day. Orally administered epiroprim combined with dapsone also prolonged survival. Thus, epiroprim is an active and potentially less toxic alternative to pyrimethamine for the treatment of toxoplasmosis.

IT **73090-70-7**, Epiroprim
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydrofolate reductase inhibitor epiroprim (Roll-8958) vs. pyrimethamine effect in acute Toxoplasma infection)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 26 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:316138 CAPLUS
DOCUMENT NUMBER: 122:72008
TITLE: Antibiotic combination containing epiroprim and

dapsone
INVENTOR(S): Kompis, Ivan; Then, Rudolf
PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, Switz.
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

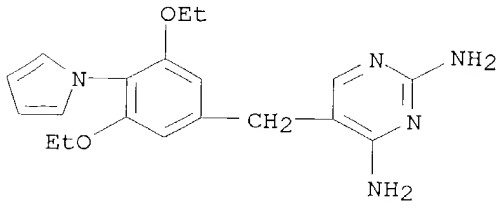
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 629403	A1	19941221	EP 1994-108767	19940608
EP 629403	B1	19980909		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5721242	A	19980224	US 1994-241887	19940512
CA 2125121	AA	19941218	CA 1994-2125121	19940603
RU 2136272	C1	19990910	RU 1994-19991	19940603
AT 170751	E	19980915	AT 1994-108767	19940608
ES 2122085	T3	19981216	ES 1994-108767	19940608
AU 9464697	A1	19941222	AU 1994-64697	19940610
AU 685449	B2	19980122		
JP 07002672	A2	19950106	JP 1994-132738	19940615
JP 2650852	B2	19970910		
CN 1105563	A	19950726	CN 1994-107507	19940616
CN 1054745	B	20000726		

PRIORITY APPLN. INFO.: CH 1993-1801 A 19930617

AB Epiroprim and dapsone, administered as a combination or sep., simultaneously or sequentially, are effective in treatment of infections with mycobacteria, actinomycetes, and Toxoplasma. Thus, administration of epiroprim and dapsone (100 and 3 mg/kg, resp.) twice a day for 14 days by gavage to mice with i.p. Nocardia infections resulted in 100% survival for >20 days.

IT **73090-70-7**, Epiroprim
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotic combination containing epiroprim and dapsone)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



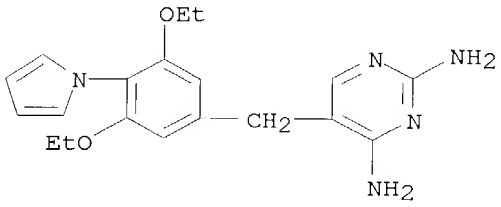
L3 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:671337 CAPLUS
DOCUMENT NUMBER: 121:271337
TITLE: Selective inhibition of dihydrofolate reductase from problem human pathogens
AUTHOR(S): Then, R.L.; Hartman, P.G.; Kompis, I.; Santi, D.

CORPORATE SOURCE: F.Hoffmann-La Roche Ltd., Basel, 4002, Switz.
SOURCE: Advances in Experimental Medicine and Biology (1993), 338(Chemistry and Biology of Pteridines and Folates), 533-6
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dihydrofolate reductase inhibitors were tested against dihydrofolate reductases from Escherichia coli, Pneumocystis carinii, and staphylococci.

IT **73090-70-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydrofolate reductase inhibitors activity against dihydrofolate reductase of Escherichia coli, Pneumocystis carinii, and staphylococci)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:524670 CAPLUS
DOCUMENT NUMBER: 121:124670
TITLE: Activity of epiroprim (Ro 11-8958), a dihydrofolate reductase inhibitor, alone and in combination with dapsone against Toxoplasma gondii
AUTHOR(S): Chang, Hernan R.; Arsenijevic, Denis; Comte, Raymonde; Polak, Annemarie; Then, Rudolf L.; Pechere, Jean-Claude
CORPORATE SOURCE: Fac. Med., Natl. Univ. Singapore, Singapore, 0511, Singapore
SOURCE: Antimicrobial Agents and Chemotherapy (1994), 38(8), 1803-7
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

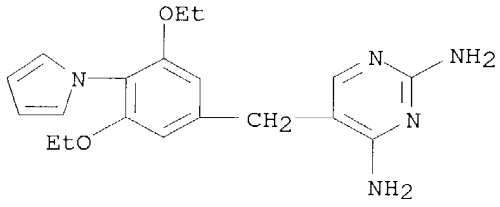
AB The authors examined the effect of epiroprim (Ro 11-898), a dihydrofolate, reductase inhibitor, alone and in combination with dapsone, against Toxoplasma gondii. In vitro, the anti-T. gondii effects of epiroprim and dapsone were observed at ng/mL levels when a 72-h uracil assay and an infection rate of one parasite per 120 macrophages were used. In combination, these drugs exerted a synergistic effect that, however, was only parasitostatic. In a model of acute infection, mice were infected i.p. with 104 parasites of the RH strain of T. gondii and were treated for 14 days by gavage (therapy divided into two daily dosages), starting 24 h after infection. Used alone, dapsone and epiroprim, each at a dose of 50 mg/kg of body weight per day, protected 10 and 0% of the mice, resp. When these drugs were administered simultaneously, a 100% survival rate was observed Pyrimethamine-sulfadiazine (4 and 250 mg/kg/day, resp.) protected

100% of the mice. A 3-wk therapy of chronically infected mice with either epiroprim (50 mg/kg/day), dapsone (50 mg/kg/day), or pyrimethamine (15 mg/kg/day) reduced the nos. of T. gondii cysts and the inflammation in their brains. A combination of epiroprim and dapsone, both at 50 mg/kg/day, further reduced the number of brain cysts in comparison with the number after the corresponding monotherapies. Epiroprim may have a role in the prophylaxis or therapy of human toxoplasmosis, especially when combined with other drugs active against T. gondii, such as dapsone.

IT **73090-70-7**, Epiroprim
RL: BIOL (Biological study)
(Toxoplasma gondii infection inhibition by dapsone and, as dihydrofolate reductase inhibitor)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 29 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:48695 CAPLUS

DOCUMENT NUMBER: 120:48695

TITLE: Dihydrofolate reductase from the pathogenic fungus Pneumocystis carinii: catalytic properties and interaction with antifolates

AUTHOR(S): Margosiak, Stephen A.; Appleman, James R.; Santi, Daniel V.; Blakley, Raymond L.

CORPORATE SOURCE: Dep. Mol. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA

SOURCE: Archives of Biochemistry and Biophysics (1993), 305(2), 499-508
CODEN: ABBIA4; ISSN: 0003-9861

DOCUMENT TYPE: Journal

LANGUAGE: English

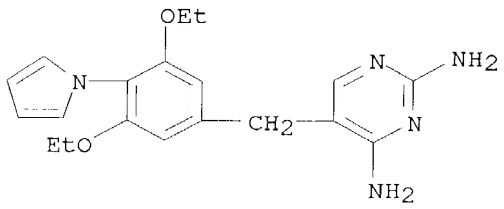
AB Dihydrofolate reductase (DHFR) from the fungus Pneumocystis carinii (pcDHFR), a target for antifolate inhibitors, has been compared with host enzyme, human DHFR (hDHFR), and with DHFR from Escherichia coli. Among the results of the considerable structural differences between pcDHFR and the other two enzymes is a much higher turnover number (kcat, 136 s-1) for pcDHFR. This is due to rapid hydride transfer from NADPH to dihydrofolate (rate constant 402 s-1), very rapid dissociation of NADP from the product complex (rate constant, koff, > 1000 s-1), and after NADPH binding, rapid dissociation of tetrahydrofolate (koff, 216 s-1). Cycling of pcDHFR is almost exclusively by this pathway. The high kcat contributes to a high Km for NADPH (9 μM) and an unusually high Km for dihydrofolate (2.5 μM). Nevertheless, the efficiency of pcDHFR is greater than DHFR from E. coli and about 25% that of hDHRF. Of seven clin. relevant inhibitors investigated, only one (trimethoprim) had a slightly lower Ki for pcDHFR than for hDHFR. The therapeutic value of trimethoprim-sulfa treatment of P. carinii infections indicates that other factors play an important role,

but the results are consistent with the frequency of complications due to toxicity of trimethoprim.

IT **73090-70-7**, Epiroprim
RL: BIOL (Biological study)
(dihydrofolate reductase of Pneumocystis carinii and human inhibition by, kinetics of)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1993:620784 CAPLUS

DOCUMENT NUMBER: 119:220784

TITLE: Development and characterization of a rapid screening assay for identifying antipneumocystis agents

AUTHOR(S): Martinez, Anthony; Kovacs, Joseph A.

CORPORATE SOURCE: Clin. Cent., Natl. Inst. Health, Bethesda, MD, 20892, USA

SOURCE: Antimicrobial Agents and Chemotherapy (1993), 37(8), 1674-8
CODEN: AMACCQ; ISSN: 0066-4804

DOCUMENT TYPE: Journal

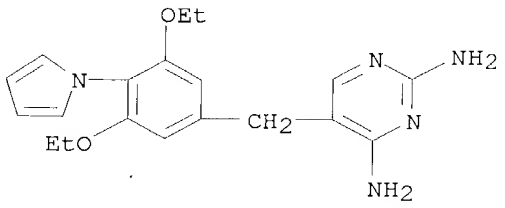
LANGUAGE: English

AB The authors developed a rapid assay for screening of compds. with potential antipneumocystis activity on the basis of incorporation of [35S]methionine into proteins newly synthesized by Pneumocystis carinii. Unambiguous evidence that P. carinii synthesizes proteins in vitro was provided by immunopptn. studies demonstrating the incorporation of [35S]methionine into the major surface glycoprotein. Treatment with two clin. active antipneumocystis agents, atovaquone (10-4 M) or pentamidine (10-4 M), prevented this incorporation. Total [35S]methionine incorporation paralleled incorporation into the major surface glycoprotein, permitting rapid assessment of anti-P. carinii activity by scintillation counting. Treatment with pentamidine (1 + 10-4 M), atovaquone, trimethoprim (1 + 10-4 M)-sulfamethoxazole (7.9 + 10-4 M), piritrexim (1 + 10-7 M), RO11-8958 (1 + 10-4 M), and amphotericin B (1 μg/mL) resulted in a greater than 67% inhibition ($P < 0.05$) of [35S]methionine incorporation. No decrease in [35S]methionine incorporation was seen with dapsone (10-5 M), trimethoprim (10-4M), recombinant mouse tumor necrosis factor (500 ng/mL), or gamma interferon. This rapid in vitro assay should be a useful adjunct in the development of new antipneumocystis agents.

IT **73090-70-7**
RL: ANST (Analytical study)
(as antipneumocystis agent, screening assay for)

RN 73090-70-7 CAPLUS

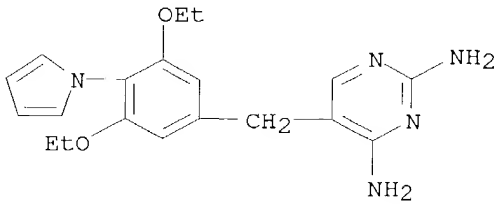
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



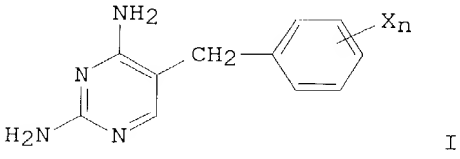
L3 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:551719 CAPLUS
DOCUMENT NUMBER: 119:151719
TITLE: Synergistic combinations of Ro 11-8958 and other dihydrofolate reductase inhibitors with sulfamethoxazole and dapsone for therapy of experimental pneumocystosis
AUTHOR(S): Walzer, Peter D.; Foy, Jilanna; Steele, Paul; White, Michael
CORPORATE SOURCE: Cincinnati Veterans Affairs Med. Cent., Cincinnati, OH, 45267, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1993), 37(7), 1436-43
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors compared Ro 11-8958, an analog of trimethoprim (TMP) with improved antimicrobial and pharmacokinetic properties, other dihydrofolate reductase (DHFR) inhibitors, sulfamethoxazole (SMX), and dapsone (DAP) in the treatment of Pneumocystis carinii pneumonia in an immunosuppressed rat model. In contrast to previous reports, high dosages of the DHFR inhibitors were used in combination with fixed, low dosages of SMX (3 mg/kg of body weight per day) or DAP (25 mg/kg/day). When administered alone at these dosages, SMX and DAP reduced the median P. carinii cyst count about 5- to 15-fold. Ro 11-8958, TMP, and diaveridine used at a dosage of 20 mg/kg/day with SMX were only slightly more effective than SMX used alone. However, administration of these DHFR inhibitors at a dosage of 100 mg/kg/day with SMX lowered the cyst count about 500- to 1,000-fold, indicating a synergistic effect. Little or no synergism was found when other DHFR inhibitors (pyrimethamine, cycloguanil, and tetroxoprim) were combined with SMX. Regimens of Ro 11-8958 at a dosage of 20 mg/kg/day with DAP and of TMP or diaveridine used at a dosage of 100 mg/kg/day with DAP showed comparable anti-P. carinii activity, lowering the cyst count 100- to 200-fold. By contrast, Ro 11-8958 administered at a dosage of 100 mg/kd/day with DAP reduced the cyst count >1,000-fold. Thus, the exptl. approach used here enables the rat model of pneumocystosis to be used to compare synergistic combinations of antifolate drugs. The favorable results achieved with Ro 11-8958 indicate that it should be considered for clin. trials.

IT **73090-70-7**
RL: BIOL (Biological study)
(sulfamethoxazole and dapsone synergy with, in treatment of pneumocystosis, in rat model)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



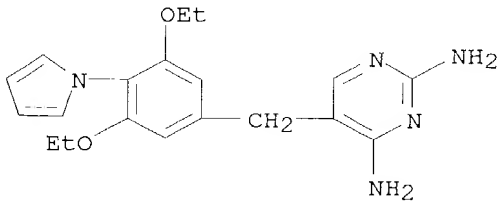
L3 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:503571 CAPLUS
DOCUMENT NUMBER: 117:103571
TITLE: Application of neural networks: quantitative structure-activity relationships of the derivatives of 2,4-diamino-5-(substituted-benzyl)pyrimidines as DHFR inhibitors
AUTHOR(S): So, Sung Sau; Richards, W. Graham
CORPORATE SOURCE: Phys. Chem. Lab., Oxford, OX1 3QZ, UK
SOURCE: Journal of Medicinal Chemistry (1992), 35(17), 3201-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A comparative study of quant. structure-activity relationships involving diaminopyrimidines (I, Xn = e.g., H, halo, alkyl, alkoxy, NO2; n = 0-3) as DHFR inhibitors using regression anal. and the neural-network approach suggests that the neural network can outperform traditional methods. The technique permits the highlighting the functional form of those parameters which have an influence on the biol. activity.

IT **73090-70-7**
RL: BIOL (Biological study)
(QSAR study of, as dihydrofolate reductase inhibitor, neural networks application in)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



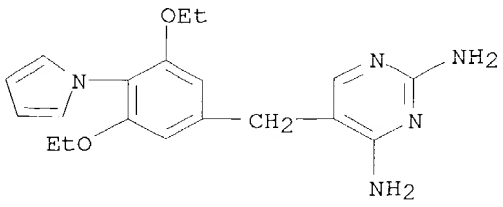
L3 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:483438 CAPLUS
DOCUMENT NUMBER: 117:83438
TITLE: Specific inhibition of Pneumocystis carinii dihydrofolate reductase and antifungal pyrimidine-derived compounds therefor
INVENTOR(S): Kompis, Ivan; Blaney, Jeffrey M.; Marlow, Charles K.
PATENT ASSIGNEE(S): Protos Corp., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9208461	A1	19920529	WO 1991-US8515	19911114
W: AT, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2095518	AA	19920515	CA 1991-2095518	19911114
ZA 9109029	A	19920826	ZA 1991-9029	19911114
EP 639075	A1	19950222	EP 1992-900837	19911114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 07509215	T2	19951012	JP 1991-502293	19911114
AU 9222027	A1	19940428	AU 1992-22027	19920831
AU 657348	B2	19950309		

PRIORITY APPLN. INFO.: US 1990-613619 19901114
US 1991-730691 19910716
WO 1991-US8515 19911114
OTHER SOURCE(S): MARPAT 117:83438

AB Pyrimidine-derived compds. (Markush included) are provided which have improved activity against fungi such as P. carinii and improved selectivity for P. carinii dihydrofolate reductase over human dihydrofolate reductase. The compds. are useful for the treatment of P. carinii pneumonia. IC50 and selectivity values for a variety of the pyrimidine derivs. are presented; the compds. had high activity and selectivity for P. carinii. 2,4-Diamino-5-(4-benzyloxybenzyl)pyrimidine a selectivity value of 53.2, compared to a selectivity for trimethoprim of 0.1).

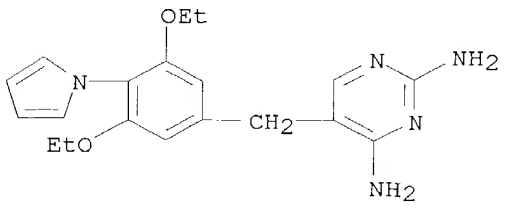
IT **73090-70-7**
RL: BIOL (Biological study)
(dihydrofolate reductase of Pneumocystis carinii inhibition by)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:38249 CAPLUS
DOCUMENT NUMBER: 114:38249
TITLE: Optimization of hydrophobic and hydrophilic substituent interactions of 2,4-diamino-5-(substituted-benzyl)pyrimidines with dihydrofolate reductase
AUTHOR(S): Dias Selassie, Cynthia; Li, Renli; Poe, Martin; Hansch, Corwin
CORPORATE SOURCE: Dep. Chem., Pomona Coll., Claremont, CA, 91711, USA
SOURCE: Journal of Medicinal Chemistry (1991), 34(1), 46-54
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Apparent K1 values were obtained from the action of 68 2,4-diamino-5-(substituted-benzyl)pyrimidines on dihydrofolate reductase (DHFR) from Escherichia coli strain MB 1428. Subsequently, these results were used to formulate appropriate QSAR's. Once again these equations emphasized the paramount importance of steric/dispersion factors in enhancing antibacterial potency. Hydrophobicity also plays a role, albeit a minor one. Comparisons with the QSAR obtained vs. prokaryotic DHFR demonstrated subtle differences in binding behavior between meta and para substituents which may be effectively maximized in the design of more efficacious and selective antibacterial agents. The bacterial and avian QSAR equations can be used to calculate selectivity indexes for trimethoprim, tetroxoprim, and 2 other specially designed 2,4-diamino-5-(substituted-benzyl)pyrimidines.

IT **73090-70-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(dihydrofolate reductase of Escherichia coli inhibition by, QSAR study of)
RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



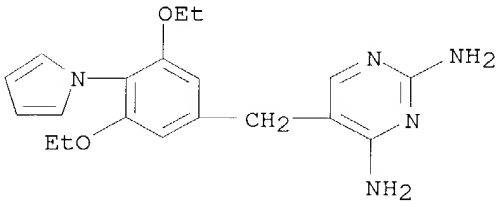
L3 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:15928 CAPLUS

Correction of: 1989:449898
DOCUMENT NUMBER: 112:15928
Correction of: 111:49898
TITLE: On the structure selectivity problem in drug design. A comparative study of benzylpyrimidine inhibition of vertebrate and bacterial dihydrofolate reductase via molecular graphics and quantitative structure-activity relationships
AUTHOR(S): Selassie, Cynthia Dias; Fang, Zhaoxia; Li, Renli; Hansch, Corwin; Debnath, Gargi; Klein, Teri; Langridge, Robert; Kaufman, Bernard T.
CORPORATE SOURCE: Dep. Chem., Pomona Coll., Claremont, CA, 91711, USA
SOURCE: Journal of Medicinal Chemistry (1989), 32(8), 1895-905
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Quant. structure-activity relationships (QSAR) were derived for the action of 68 5-(substituted benzyl)-2,4-diaminopyrimidines on dihydrofolate reductase from Lactobacillus casei and chicken liver. The QSAR were analyzed with respect to the stereog. models of the active sites of the enzymes and were found to be in good agreement. By using these QSAR equations, the design of new trimethoprim-type antifolates having higher selectivity for the bacterial enzyme was attempted. The general problem of developing selective inhibitors is discussed.

IT **73090-70-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of and dihydrofolate reductase of bacteria inhibition by, structure in relation to)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



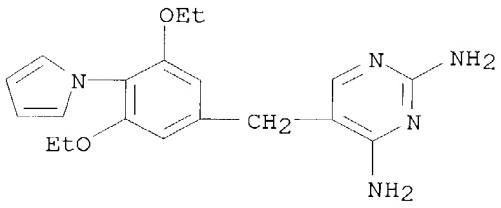
L3 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:449898 CAPLUS
DOCUMENT NUMBER: 111:49898
TITLE: On the structure selectivity problem in drug design. A comparative study of benzylpyrimidine inhibition of vertebrate and bacterial dihydrofolate reductase via molecular graphics and quantitative structure-activity relationships
AUTHOR(S): Dias Selassie, Cynthia; Fang, Zhaoxia; Li, Renli; Hansch, Corwin; Debnath, Gargi; Klein, Teri; Langridge, Robert; Kaufman, Bernard T.
CORPORATE SOURCE: Dep. Chem., Pomona Coll., Claremont, CA, 91711, USA
SOURCE: Journal of Medicinal Chemistry (1989), 32(8), 1895-905
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Quant. structure-activity relationships (QSAR) were derived for the action of 68 5-(substituted benzyl)-2,4-diaminopyrimidines on dihydrofolate reductase from Lactobacillus casei and chicken liver. The QSAR were analyzed with respect to the stereog. models of the active sites of the enzymes and were found to be in good agreement. By using these QSAR equations, the design of new trimethoprim-type antifolates having higher selectivity for the bacterial enzyme was attempted. The general problem of developing selective inhibitors is discussed.

IT **73090-70-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of and dihydrofolate reductase of bacteria inhibition by, structure in relation to)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]-(9CI) (CA INDEX NAME)



L3 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1986:182242 CAPLUS

DOCUMENT NUMBER: 104:182242

TITLE: Inhibition of chicken liver dihydrofolate reductase by 5-(substituted benzyl)-2,4-diaminopyrimidines. A QSAR and graphics analysis

AUTHOR(S): Selassie, Cynthia Dias; Fang, Zhao Xia; Li, Ren Li; Hansch, Corwin; Klein, Teri; Langridge, Robert; Kaufman, Bernard T.

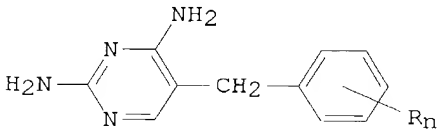
CORPORATE SOURCE: Dep. Chem., Pomona Coll., Claremont, CA, 91711, USA

SOURCE: Journal of Medicinal Chemistry (1986), 29(5), 621-6
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I, R=H, halo, alkyl alkoxy, etc., n=1-3

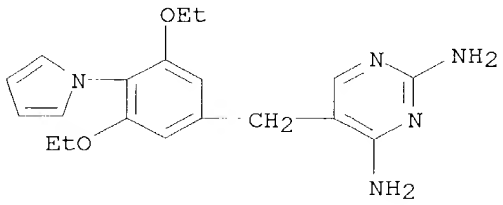
AB The inhibition of chicken liver dihydrofolate reductase by a series of substituted benzylpyrimidines (I) was investigated. From the Ki values, a QSAR was formulated. This math. model was compared with mol. graphics models constructed from the x-ray crystallog. coordinates of trimethoprim and 5-(3,4-dimethoxy-4-isopropenylbenzyl)-2,4-diaminopyrimidine bound to

the enzyme. There was good correspondence between the 2 types of models.

IT **73090-70-7**
RL: BIOL (Biological study)
(dihydrofolate reductase of chicken liver inhibition by, kinetics of, QSAR study of)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1982:544216 CAPLUS

DOCUMENT NUMBER: 97:144216

TITLE: Partition coefficients of 5-(substituted benzyl)-2,4-diaminopyrimidines

AUTHOR(S): Seiler, P.; Bischoff, O.; Wagner, R.

CORPORATE SOURCE: Cent. Res. Units, F. Hoffmann-La Roche Cie., Basle, Switz.

SOURCE: Arzneimittel-Forschung (1982), 32(7), 711-14
CODEN: ARZNAD; ISSN: 0004-4172

DOCUMENT TYPE: Journal

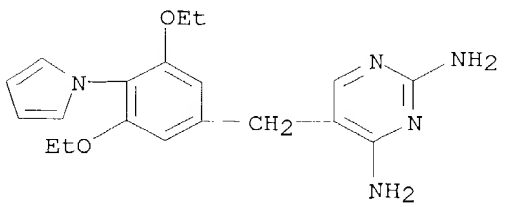
LANGUAGE: English

AB The pK of 19 and the partition coeffs. (P) of seventy-nine 5-benzyl-2,4-diaminopyrimidines substituted in the benzene ring moiety were exptl. determined A multiple regression anal. shows that P cannot be calculated with reasonable accuracy starting from fragmental consts. Interactions between substituents can reduce P by an order of magnitude below those obtained by applying Hansch's and Rekker's models. Interaction terms between different substituents were calculated

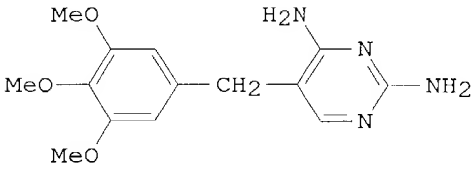
IT **73090-70-7**
RL: PRP (Properties)
(protonation consts. and partition coeffs. of, between water and n-octanol, deviations in LFER calcn. of)

RN 73090-70-7 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 39 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1982:466049 CAPLUS
DOCUMENT NUMBER: 97:66049
TITLE: New analogs of trimethoprim
AUTHOR(S): Then, Rudolf L.; Bohni, Erika; Angehrn, Peter; Plozza-Nottebrock, Helene; Stoeckel, Klaus
CORPORATE SOURCE: Pharm. Res. Dep., F. Hoffmann-La Roche and Co., Ltd., Basel, CH-4002, Switz.
SOURCE: Reviews of Infectious Diseases (1982), 4(2), 372-7
CODEN: RINDDG; ISSN: 0162-0886
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

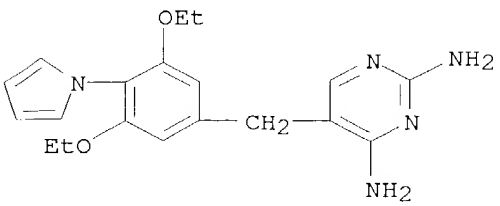


I

AB Possible goals and recent developments in he field of antimicrobial 2,4-diamino-5-benzylpyrimidines are discussed. Three analogs of trimethoprim (I) all bearing different substituents at position 4 of the benzyl moiety and one also having the methoxy groups replaced by ethoxy substituents are characterized in some detail. These analogs exhibit physicochem. properties different from those of trimethoprim and are potent inhibitors of several dihydrofolate reductases. Because they differ from trimethoprim in lipophilicity, their in vitro activity, spectrum of activity, and pharmacokinetic properties also differ from those of trimethoprim. These differences are judged to be the reason for enhanced in vivo efficacy against exptl. infections. Distinct pharmacokinetic differences observed in dogs include a longer elimination half-life and a larger volume of distribution. These favorable properties indicate the potential value of further studies in humans.

IT **73090-70-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)

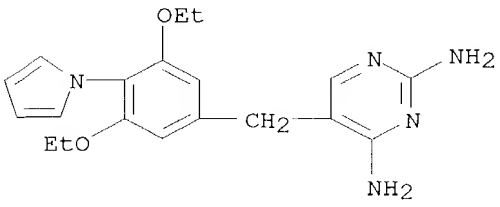


L3 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1981:170109 CAPLUS
DOCUMENT NUMBER: 94:170109
TITLE: 2,4-Diamino-5-benzyl-pyrimidines as inhibitors of dihydrofolate reductase
AUTHOR(S): Kompis, I.; Then, R.; Wick, A.; Montavon, M.
CORPORATE SOURCE: Pharm. Res. Dep., F. Hoffmann-La Roche Co. Ltd., Basel, CH-4002, Switz.
SOURCE: Enzyme Inhibitors, Proc. Meet. (1980), 177-89. Editor(s): Brodbeck, Urs. Verlag Chem.: Weinheim, Fed. Rep. Ger.
CODEN: 45FGAU
DOCUMENT TYPE: Conference
LANGUAGE: English

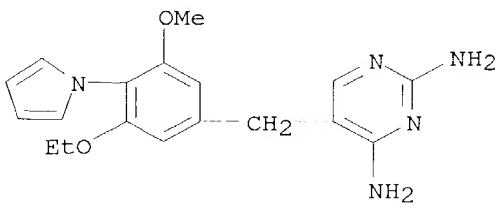
AB 2,4-Diamino-5-(3',5'-dialkoxybenzyl)pyrimidines substituted at C(4') with halogen, N, or functionalized C atoms were synthesized and tested for their relative inhibitory activity against dihydrofolate reductases (EC 1.5.1.3) from Echerichia coli and rat liver. Compds. with halogen or N substitution in position 4 of the benzyl ring showed high inhibitory activities with the E. coli enzyme in comparison to trimethoprim. With the exception of the carboxylic acid derivative, most of the compds. containing functionalized C substituents possessed a relatively high affinity for the E. coli enzyme. The most active substance in this series was the 4'-isopropenyl derivative; it was also the most highly selective for the E. coli enzyme relative to the liver enzyme. Substitution of 1 or both methoxy groups with ethoxy groups resulted in derivs. with higher activity towards bacterial enzyme compared to dimethoxy derivs. but decreased selectivity. However, several of these compds., especially the 3',5'-diethoxy-4'-pyrrolo derivative, were superior to trimethoprim in both of these criteria. The inhibition of dihydrofolate reductases of other bacteria and protozoa by several by these compds. was also tested.

IT **73090-70-7 77453-36-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(dihydrofolate reductase inhibition by, structure in relation to)

RN 73090-70-7 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3,5-diethoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 77453-36-2 CAPLUS
CN 2,4-Pyrimidinediamine, 5-[[3-ethoxy-5-methoxy-4-(1H-pyrrol-1-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)


OMe
N
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NH2
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NH2